

IN THE CLAIMS:

Please cancel claims 9, 19, 54 and 57 without prejudice.

Kindly amend claims 1, 7, 8, 10, 11, 12, 24, 25, 52, 55, 58, 64, 68, 75 and 77 as follows.

1. (Amended) A peptide conjugate comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bonded by its N terminus to the C terminus end of X wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof.

P2
7. (Amended) A peptide conjugate according to claim 1, wherein each amino acid unit in Z is Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid or Met.

P3
8. (Amended) A peptide conjugate according to claim 7, wherein each amino acid unit in Z is Glu, Lys or Met.

P3
10.(Amended) A peptide conjugate according to claim 1, wherein Z is (Lys)_n, wherein n is an integer in the range from about 4 to about 15.

P4
11. (Amended) A peptide conjugate according to claim 9, wherein Z is Lys4 (SEQ ID NO: 55), Lys5 (SEQ ID NO: 56) or Lys6 (SEQ ID NO: 62).

12. (Amended) A peptide conjugate according to claim 11, wherein Z is Lys₆ (SEQ ID NO: 62).

P5
24. (Amended) The peptide conjugate according to claim 1 or 10, wherein X is selected from the group consisting of enkephalin, Leu-enkephalin, Met-enkephalin, angiotensin I, angiotensin II, vasopressin, endothelin, vasoactive intestinal peptide, neuropeptides, endorphins, insulin, gramicidin, para-celsin, delta-sleep inducing peptide, gonadotropin-Releasing hormone, human parathyroid hormone (1-34), EMP-1, Atrial natriuretic peptide (ANP, ANF), human brain natriuretic peptide (hBNP), cecropin, kinetinsin, neuropeptides, elafin, guamerin, atriopeptin I, atriopeptin II, atriopeptin III, deltorphin I, deltorphin II, vasotocin, bradykinin, dynorphin, dynorphin A, dynorphin B, growth hormone release factor, growth hormone, growth hormone releasing peptide, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide II, growth hormone releasing peptide, tachykinin, adrenocorticotrophic hormone (ACTH), brain natriuretic polypeptide, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, galanin, gastric releasing polypeptide, gastric inhibitory polypeptide, gastrin, gastrin releasing peptide, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, LHRH, melanin concentrating hormone, melanocyte stimulating hormone (MSH),

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alpha-MSH, morphine modulating peptides, motilin, neurokinin A, neurokinin B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, pituitary adenylate cyclase activating polypeptide (PACAP), pancreatic polypeptide, peptide YY, peptide histidine-methionine amide (PHM), secretin, somatostatin, substance K, thyrotropin-releasing hormone (TRH), kyotorphin, melanostatin (MIF-1), thrombopoietin analogs, in particular AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO: 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO: 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 17), insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO: 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH₂) (SEQ ID NO: 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO: 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO: 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO: 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-

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Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO: 31), Melanotan-II
(also known as MT-II, alpha-MSH4-10-NH₂, or Ac-Nle⁴-Asp⁵-His⁶-D-Phe⁷-Arg⁸-Trp⁹-
Lys¹⁰) (SEQ ID NO: 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-
Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID
NO: 33), ornipressin (also known as 8-ornithine-vasopressin, (POR-8), vasopressin), Cys-Phe-
Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH₂, Disulfide bridge: Cys1-Cys6) (SEQ ID NO: 34), octreotide
(201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID
NO: 35), eptifibatide (INTEGRILIN), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-
Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-
Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH₂; Disulfide bridge: Cys2-Cys7)
(SEQ ID NO: 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH₂ (SEQ ID NO: 37); endomorphin-2
Tyr-Pro-Phe-Phe-NH₂ (SEQ ID NO: 38), nociceptin (also known as Orphanin FQ, Phe-Gly-
Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO: 39),
angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO:
40), adrenomedullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID
NO: 41), antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO: 42),
Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH₂), indolicidin (Ile-Leu-Pro-Trp-Lys-
Trp-Pro-Trp-Pro-Trp-Arg-Arg-NH₂) (SEQ ID NO: 43), osteocalcin (37-49) (Gly-Phe-Gln-
Gly-Ala-Tyr-Ala-Phe-Tyr-Gly) (SEQ ID NO: 44), rat tat-20 (1-13) (Gln_n) Clu

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25. (Amended) A peptide conjugate according to claim 1 wherein the conjugate is

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Lys₆-NH₂ (GHRH(1-44)(Human)-Lys₆-NH₂) (SEQ ID NO: 88);

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Glu₆-NH₂ (GHRH (1-44)(Human)-Glu₆-NH₂) (SEQ ID NO: 89);

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H- Lys₆-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH (Lys₆-PTH(1-34)(Human)-OH) (SEQ ID NO: 90);

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-Lys₆-OH (PTH(1-34)(Human)-Lys₆-OH) (SEQ ID NO: 91);

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys₆-OH (GLP-1-(7-36)(Human)-Lys₆-OH) (SEQ ID NO: 92);

H-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys₆-OH (EMP-1-Lys₆-OH) (SEQ ID NO: 93);

H- Lys₆-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly- Lys₆-OH (Lys₆-EMP-1- Lys₆-OH) (SEQ ID NO: 95);

H-Aib-His-2-D-Nal-D-Phe-Lys-(Lys)₆-NH₂ (GHRP-(Lys)₆-NH₂) (SEQ ID NO: 96);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Lys-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Lys-Glu-Glu-Glu-Lys-OH) (SEQ ID NO: 97);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Glu-Glu-Glu-Lys-OH) (SEQ ID NO: 98);

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Anchored*
H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-(Lys-Glu)₃) (SEQ ID NO: 99);

H-Tyr-Gly-Gly-Phe-Leu-(Dpr)₆-OH (Leu-enkephalin-(Dpr)₆-OH) (SEQ ID NO: 100);

H-Lys₆-Tyr-Gly-Gly-Phe-Leu-OH (H-Lys₆-Leu-enkephalin) (SEQ ID NO: 101);

H-Tyr-Gly-Gly-Phe-Leu- Lys₆-OH (H-Leu-enkephalin-Lys₆) (SEQ ID NO: 11);

H-Lys₆-Tyr-Gly-Gly-Phe-Leu-Lys₆-OH (H-Lys₆-Leu-enkephalin-Lys₆-OH) (SEQ ID NO: 102);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys)₆-OH (GnRH-Lys₆-OH) (SEQ ID NO: 103);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys-Glu)₃-OH (GnRH-(Lys-Glu)₃-OH) (SEQ ID NO: 104); and

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-(Lys-Glu)₃-OH (PTH 1-34 human-Lys₆-Glu₁-OH) (SEQ ID NO: 105)

52. (Amended) A peptide conjugate comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 3; or a salt thereof.

55. (Amended) The peptide conjugate of claim 1, wherein Z consists of about 4 to about 7 amino acid units.

58. (Amended) The peptide conjugate of claim 1, wherein Z comprises at least five Lys amino acid units.

64. (Amended) A peptide conjugate comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof, wherein said pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units.

68. (Amended) A peptide conjugate comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein Z is Lys_p-Xaa_q or Xaa_p-Lys_q, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 4-15, and each Xaa is Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid or Met; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof,

wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO: 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO: 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 17) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO: 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO: 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO: 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO: 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO: 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2) (SEQ ID NO: 25), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO: 26), epidermal growth factor (20-

31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO: 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO: 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO: 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO: 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO: 31), Melanotan-II (MT-II, alpha-MSH4-10-NH₂, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO: 32), thymosin alphal (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO: 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH₂, Disulfide bridge: Cys1-Cys6) (SEQ ID NO: 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO: 35), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH₂; Disulfide bridge: Cys2-Cys7) (SEQ ID NO: 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH₂ (SEQ ID NO: 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH₂ (SEQ ID NO: 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO: 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO: 40), adrenomedullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO: 41), antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO: 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH₂), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH₂) (SEQ ID NO: 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO: 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO: 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO: 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO: 49), leptin (93-105) (Asn-Val-

Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO: 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH₂) (SEQ ID NO: 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH₂) (SEQ ID NO: 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO: 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO: 54), and Leupeptin (Ac-Leu-Leu-Arg-CHO).

F10
Conclude

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75. (Amended) A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to stimulate erythropoiesis.

F12

77. (Amended) The peptide conjugate of claim 1, wherein the conjugate is represented by the following sequence: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-(Lys)₆-NH₂ (SEQ ID NO: 122) or a fragment thereof.

Please add the following new claims 78-81 as follows:

F13

78. (New) A peptide conjugate consisting of X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bonded by its N terminus to the C terminus end of X wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I

Excludes Trp, Pro, Cys



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-

alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof.

79. (New) A peptide conjugate consisting of X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with

carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 3; or a salt thereof.

80. (New) A peptide conjugate consisting of X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I



wherein R¹ and R² are selected from the group consisting of hydrogen, C₁₋₆-alkyl, phenyl, and phenyl-methyl, wherein C₁₋₆-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R¹ and R² together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof, wherein said pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units.

81. (New) A peptide conjugate consisting of X and Z,

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wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein Z is Lys_p-Xaa_q or Xaa_p-Lys_q, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 4-15, and each Xaa is Ser, Thr, Tyr, Asn, Gln, Asp, Glu; Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid or Met; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the

corresponding pharmacologically active peptide sequence X, when treated with

carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least 2; or a salt thereof,

wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO: 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO: 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 17) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO: 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO: 21),

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Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO: 26), epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO: 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO: 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO: 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO: 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO: 31), Melanotan-II (MT-II, alpha-MSH4-10-NH₂, or Ac-Nle⁴-Asp⁵-His⁶-D-Phe⁷-Arg⁸-Trp⁹-Lys¹⁰) (SEQ ID NO: 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO: 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH₂, Disulfide bridge: Cys1-Cys6) (SEQ ID NO: 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO: 35), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH₂; Disulfide bridge: Cys2-Cys7) (SEQ ID NO: 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH₂ (SEQ ID NO: 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH₂ (SEQ ID NO: 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO: 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO: 40), adrenomedullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO: 41), antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO: 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH₂), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH₂) (SEQ ID NO: 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO: 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO: 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO: 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 48), fibrinogen binding inhibitor peptide (His-